incapable of eliciting an effective immunoinhibitory response in the vertebrate. It must be undisputed that those skilled in the art would understand what an endogenously synthesized peptide from a vertebrate would be. Treatises are written on the subject and are well known and need not be specifically cited here. Whether such peptides are vital or not is immaterial. For example, the function specifically inhibited by the fusion protein specifically set forth in the examples, is considered vital to reproduction. However, the art is replete with examples of the use of such peptides on their own to diminish function in a therapeutic manner. Likewise, peptides having activity which can be inhibited as a result of an immune response are well known in the art. Finally, the prior art, including the publications cited in the Office Action herein, clearly recognize proteinaceous portions of peptides which by themselves are incapable of eliciting an effective immunoinhibitory response in a vertebrate. Hence, it must be undisputed that the limitations defining the claimed first proteinaceous portion are well known in the art. Absent a specific recitation of sources in the Office Action demonstrating the indefiniteness of the claimed limitations, it must be undisputed that the limitations set forth in the independent claims, and therefore, the rejected dependent claims, are well known and quite definite to those skilled in the art. Hence, it is respectfully submitted that Applicants have overcome the grounds for rejection under 35 USC 112, second paragraph.

Claims 1-3, 11, 13 and 16 were rejected under 35 USC 112, first paragraph, on the grounds that while the claims are enabled for a fusion protein that inhibits the function in the class of gonadotropins and BHV, the claims are not enabled for a fusion protein that inhibits the function of any endogenously made protein and protects against any disease in a vertebrate. It is undisputed that the claims are drawn to eliciting a dual immune response against a fusion protein that is specifically defined in the claims. An immune response against a portion of the fusion protein inhibits the activity of an endogenous protein specifically defined as discussed above, and another portion is used to elicit an immune response against a pathogen, which is capable of pathogenically infecting the vertebrate. It is the portion causing the immunogenicity to the pathogen that protects the vertebrate from infection by the pathogen while also inhibiting the activity of the endogenous peptide which would otherwise not be immunogenic if solely administered to the vertebrate. These results occur when the vertebrate is vaccinated with an effective amount of the fusion protein. The Office Action holds that the specification does not describe the structure or function for all the possible proteins made in a vertebrate, or what result of inhibiting the function of any protein would do to the vertebrate when administered, except for GnRH. The Office Action further generally holds that the specification does not illustrate that incorporating any protein from any pathogen into the claimed fusion protein protects against every disease.

The issue is whether one skilled in the art would be required to use an undue amount of experimentation to inhibit every protein made in a vertebrate while protecting against every

disease that may be encountered by a vertebrate by administering the claimed fusion protein. It is respectfully submitted that the claim is being interpreted beyond the actual words of the claim.

Independent Claims 1 and 3 claim a first proteinaceous portion defined by three limitations as discussed above. Examples of such proteinaceous portions which are analogous to all or part of a peptide are well known in the art. A non-exhaustive list of such peptides are set forth in the specification. Absent general statements made in the Office Action, there are no specific references indicating that such peptides are not well known in the art and well defined in the art. The prior art cited by the Examiner is an example of such peptides known to immunologists and microbiologists. A list of such peptides would be exhaustive. However, simply because the list of peptides is exhaustive does not mean that those skilled in the art would not be able to recognize what such peptides are. Absent specific evidence of such confusion in the art, one skilled in the art would have no problem picking up any immunology text wherein chapters on such peptides are written, and be able to understand the genus of those peptides. Likewise, the microbiology and immunology art are replete with examples and in-depth knowledge of immunogenic proteinaceous portions from pathogens. To hold that such peptides endogenously synthesized within vertebrates and/or proteinaceous portions analogous to all or part of an immunogen from a pathogen are not well known to those skilled in the art is to hold that the aforementioned texts on microbiology and immunology do not exist. One skilled in the art looking to make and use the present invention need only pick up a microbiology and/or immunology text to be able to recognize the proteinaceous portions set forth specifically in subparagraphs (a) and (b) in independent Claims 1 and 3, and therefore, as set forth in dependent claims dependent thereupon, to be able to make and use the present invention. Absent specific recitations in such texts to the contrary, it must be held that the Office Action does not provide a basis in fact or in law for a holding of non-enablement.

Independent Claims 1 and 3 were rejected under 35 USC 103(a) as being unpatentable over the United States Patent 5,684,145 to Van Der Zee et al. and the Mittal et al. reference for the reasons previously set forth in the Office Action dated December 27, 2000. The Office Action raises issues of fact and issues of law. The issues of fact relate to the exact scope of the teaching of the prior art. The issue of law is whether or not there is a suggestion in the prior art references for their combination to derive the presently claimed invention.

With regard to the factual issues related to the teaching of the prior art, it is undisputed that the Van Der Zee et al. reference discloses a carrier system for use in vaccination of mammals against GnRH. The cited patent only discloses a vaccine including a GnRH peptide conjugated to *E. coli* fimbrial-filaments. An immune response is elicited against GnRH. It is undisputed that it was previously known that GnRH itself is not immunogenic and that it requires an immunogenic carrier to elicit an effective immune response solely against GnRH. It is also undisputed that the Van Der Zee et al. reference does not disclose or even suggest utilizing

GnRH in a fusion protein for producing a dual immune response. Likewise, it is undisputed that the Mittal et al. reference discloses an adenovirus recombinant expressing full (gD) or truncated form (tgD) of the glycoprotein gD gene of BHV-1. It is further admitted as being undisputed that gD is antigenic on its own. However, it must also be undisputed that the Mittal et al. reference does not disclose or even suggest the use of gD as a fusion protein, as a carrier, or in any way as part of a fusion protein for inducing a dual immune response in a vertebrate. Although the Office Action states, in conclusion, that one of skill in the art could use such an antigenic protein as a carrier or part of a fusion protein, no reference in support is provided. Hence, there is absolutely no evidence of record that suggests the modification of the teaching of the cited references to derive a fusion protein.

The scientific facts set forth in the cited references provide evidence of knowledge of one of skill in the art. However, they do not provide evidence beyond the statements made in the references. The Van Der Zee et al. patent only discloses GnRH peptide conjugated to the *E. coli* carrier. The Mittal et al. reference only discloses a full-length form of gD from BHV-1 inserted into a human adenovirus type 5 vector. Neither reference discloses or suggests a fusion protein in general, or a fusion protein for producing a dual immune response. There is no suggestion in any reference cited for combining either GnRH or gD into a fusion protein to produce a dual immune response. These facts gleaned from the references must be undisputed.

The Office Action accurately cites *In re Fine* to hold that obviousness can only be established by combining or modifying the teaching of the prior art to produce the claimed invention where there is some teaching suggestion or motivation to do so in the references themselves or in knowledge generally available to one of ordinary skill in the art. However, references must be cited as a basis for the knowledge of those skilled in the art. The issue is not whether a combination of references is obvious to the United States Patent Office but rather if it would be obvious to one of skilled in the art.

The only way of proving obviousness to one of skilled in the art is by specific citations to references demonstrating the same. In order to provide a basis for a *prima facie* obviousness type rejection, a factual basis must be found in the prior art at least describing a fusion protein that produces a dual immune response. Absent such a recitation of the prior art, there is absolutely no motivation to one desiring a dual response to create the fusion protein. Rather, one would read the cited references and administer the carrier system disclosed in the Van Der Zee et al reference and then either prior thereto or subsequent thereto administer the vehicles disclosed in the Mittal et al reference. The Office Action is silent with regard to any prior art reference suggesting that one of skilled in the art do any other administration or modification of the references. Absent such evidence of record, it is respectfully submitted that the Office Action failed to set forth a basis for a *prima facie* obviousness rejection.

If it is held that the *prima facie* rejection is substantiated, *arguendo*, then it is respectfully submitted that the specification as filed provides factual evidence rebutting the *prima facie* obviousness rejection. Specifically, the prior art references teach for individual immunization of antigenic substances. The Van Der Zee et al reference specifically teaches that since GnRH is non-immunogenic, it should be combined with at least a part of a *E. coli* P-fimbrial filament in a specific position. Criticality is stated in the cited patent regarding at least one antigenic determinant for GnRH or an analog or derivative of GnRH be located at a specific cite because exposure of the antigenic cite is hypercritical to immunogenicity. This is the crux of the Van Der Zee et al patent. The Mittal et al reference relates solely to expression of immunogenicity to the glycoprotein gD. The desire stressed in the Mittal et al reference is to lower the cost of vaccine production. Adenovirus-vectored vaccines are the alternative addressed in the Mittal et al reference. As stated on page 306 of the Mittal et al reference, the critical or significant observations are that the form of the antigen produced by the vector can greatly influence the immune response and the replication-incompetent recombinants appear to be effective vectors for the induction of immunity and therefore should provide vaccines that are environmentally extremely safe. Again, as set forth in the Van Der Zee et al reference, criticality is given to the form of the antigen produced. It is not at all obvious to one of skilled in the art that a fusion of two peptides will result in a single immunogenic response. Both the Van Der Zee et al and Mittal et al reference were only looking at single immune response.

The example set forth in the presently pending application provide evidence of unexpected results, the results being unexpected based upon the teachings of the cited references. Specifically, although criticality is given with regard to the form of the antigen produced vis-à-vis the immune response obtained in the cited references, the present invention provides factual evidence in the form of data demonstrating that the present invention can achieve a fusion of two proteinaceous portions and yet also achieve an immunogenic response to each of those two portions. Based on the specific criticalities set forth in the cited prior art references, this factual evidence demonstrates unexpected results not at all obtainable or suggested by the prior art reference. The prior art specifically combines antigenic proteins with a carrier or adjuvant to produce a single antigenic response. This was unexpected based on the publication cited. The present invention fuses two antigenic proteins to obtain a dual response, highly unexpected in view of the prior art providing a surprising single response. The data set forth in the examples of the presently pending application and specifically those examples set forth in example 3 demonstrating immunization of mice, provides a factual rebuttal to the *prima facie* rejection, if such a rejection, *arguendo*, is held. Hence, it is respectfully submitted that, as a matter of law, the *prima facie* rejection has been overcome.

In view of the above, it is respectfully submitted that there is no basis in fact or law supporting the *prima facie* rejection of the independent claims. Moreover, if the *prima facie* is

held to have a basis as set forth in the specification, *arguendo*, then Applicants have provided a factual evidence as a basis for a rebuttal of the *prima facie* rejection. Hence, it is respectfully submitted that the independent claims are apparently distinguishable over the prior art.

The remaining dependent claims not discussed above ar ultimately dependent upon at least one of the independent claims discussed above. No prior art reference makes up for the deficiencies of that reference as applied against the independent claims as no prior reference discloses or suggests the invention as set forth in the independent claims, as discussed in detail above. Such a combination of references that derive the present invention can only be made through hind sight as no prior art reference discloses or even suggest the fusion protein of the present invention, as discussed in detail above.

In view of the above, the application is in condition for allowance which allowance is respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

KOHN & ASSOCIATES

Kenneth I. Kohn
Registration No. 30,955
30500 Northwestern Highway
Suite 410
Farmington Hills, Michigan 48334
(248) 539-5050

Dated: April 2, 2002

CERTIFICATE OF MAILING

Express Mail Mailing Label No.: EV 056 056 045 US
Date of Deposit: April 2, 2002

I hereby certify that this correspondence is being deposited with the United States Postal Service as "Express Mail Post Office To Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Marie M. DeWitt